REMARKS

Formal Matters

Claims 13, 16-22 are pending after entry of the amendments set forth herein.

Claim 13 was examined. Claim 13 was rejected. No Claims were allowed.

Claims 1-12 and 14-15 have been canceled.

Claim 13 has been amended. Support for the amendment is found in the claims as originally filed, as well as in the specification at, for example, original claim 1, paragraph [0097], bridging pages 19 to 20, and paragraph [00193], bridging pages 45 to 46.

New Claims 16-22 have been added. Support for the new claims is found in the claims as originally filed, as well as in the specification at, for example: Claim 16: original claim 2; Claim 17: paragraph [0075], page 15; Claim 18: original claim 6; Claim 19: original claim 7; Claim 20: original claim 8; Claim 21: original claim 9; and Claim 22: original claim 10.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Rejection under 35 U.S.C. §102(b)

Claim 13 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Gether et al., EMBO Journal 16:6737-6747, 1997 (*hereinafter* "Gether et al."). In view of the amendments to the claims and the remarks put forth below, this rejection is respectfully traversed as applied and as it may be applied to the pending claims.

In particular, the Office Action states the following:

> Gether et al. teach a method for directly monitoring conformational changes in a G protein coupled receptor, beta2 adrenergic receptor (a MSST) induced by an agonist or an antagonist. The beta2 adrenergic receptor was covalently labeled by a cysteine-selective and environmentally sensitive, fluorescent probe, N,N'-dimethyl-N-(iodoacetyl0-N'-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)ethylenediamine (IANBD). Gether et al. also teach attachment of IANBD to amino acid residues of the confirmationally sensitive regions, including ^{265}Cys in the third intracellular loop (See, e.g., Abstract;

Figs. 1 and 2; and Table I). Since the measurement of fluorescence was done in a cuvette (see cited reference of Gether et al, J.B.C 270:28268-28275, 1995), the beta2 adrenergic receptor would be attached to the cuvette (a immobilization phase), via either the N-terminal portion or C-terminal portion. Gether et al. further teach purification the receptors by nickel-column chromatography using chelating Sepharose (see purification procedures at page 6745). Thus, the reference of Gether et al. meets the limitations of claim 13.

Without conceding to the correctness of the rejection and in the spirit of expediting prosecution, Claim 1 has been amended to recite a "a membrane-spanning, signal-transducing protein (MSST) comprising a conformationally-sensitive detectable probe positioned on or within a conformationally sensitive region of the MSST protein, with the proviso that **no probe** is positioned in a transmembrane domain". Support for the amendment can be found in the claims as originally filed, as well as in the specification at, for example: original claim 1, paragraph [0097], bridging pages 19 to 20, and paragraph [00193], bridging pages 45 to 46.

In contrast to the presently claimed invention, Gether discloses a series of labeled mutant GPCRs that were produced using the detectable label IANBD (a fluorophore capable of labeling cysteine residues in an apolar environment), which resulted in detectable labeling of cysteines at positions within the third intracellular domain **as well as detectable labeling of positions within the transmembrane domain**. Accordingly, Gether et al., does not disclose a GPCR that is labeled with a conformationally detectable probe on the conformationally sensitive third intracellular domain of the GPCR, **without such a probe being also positioned in a transmembrane domain of the receptor**.

The labeled mutant-GPCR disclosed in Gether et al., (Table 1, last line) and noted in the Office Action (Page 3) includes a detectable label at position 265, which is in the third intracellular domain. However, the mutant GPCR of Gether et al. **also includes** detectable label at positions 77, 116, and 237, which are all located in the transmembrane domain. Currently, amended Claim 13 recited "**no probe** positioned in a transmembrane domain". Therefore, the labeled mutant and wild-type GPCRs of Gether et al. are not the same as the membrane spanning, signal transducing proteins of Claim 13.

Accordingly, since Gether et al. fails to teach each and every element as set forth in the claims, the cited reference fails to anticipate the claimed invention as presented in the Office Action. Moreover, Gether et al., also fails to teach or suggest labeling of membrane spanning, signal transducing proteins on or within the third intracellular domain while not labeling on or within the transmembrane domain.

In view of the above, the Applicants respectfully request that the rejection of claim 13 under 35 U.S.C. §102(b) be withdrawn.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-213CIP.

Respectfully submitted,
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